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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Biotechnology Activities; Recombinant DNA Research: Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

AGENCY: National Institutes of Health (NIH), Department of Health and Human Services (HHS).

ACTION: Notice of changes to the NIH Guidelines.

SUMMARY:

Concerns about the emergence of a pandemic influenza virus have spurred research with influenza viruses that have the potential to cause a pandemic, such as highly pathogenic avian influenza (HPAI) H5N1 viruses. In 2012, two published studies funded by the National Institutes of Health (NIH) examined genetic changes that would allow HPAI H5N1 viruses to transmit by respiratory droplets among ferrets, an animal model that is often used to predict transmission and pathogenicity of influenza viruses in humans. This research raised concerns regarding the potential for HPAI H5N1 viruses to evolve and lead to a global pandemic. If transmission of a genetically engineered HPAI H5N1 virus among ferrets by respiratory droplets indicates that HPAI H5N1 viruses could evolve to

transmit efficiently among humans by respiratory droplets, the public health risk of such a virus would be greater than that of the HPAI H5N1 virus currently circulating in poultry and wild birds, which does not easily transmit among humans. The NIH Recombinant DNA Advisory Committee (RAC) was asked to review the biosafety requirements for recombinant research with HPAI H5N1 virus contained in the October 2011 NIH Guidelines and determine whether these conditions and practices are adequate to address research with HPAI H5N1 viruses that transmit among mammals by respiratory droplets, as demonstrated in an appropriate animal model or clinically in humans (referred throughout this document as mammalian-transmissible HPAI H5N1). On January 24, 2013, the RAC held a public meeting, together with influenza experts, as well as experts from the Centers for Disease Control and Prevention (CDC), the Biomedical Advanced Research and Development Authority (BARDA), HHS, the Food and Drug Administration (FDA), the World Health Organization (WHO), and the U.S. Department of Agriculture (USDA). The RAC recommended additional enhancements for research on mammalian-transmissible HPAI H5N1 virus to supplement the biosafety requirements for HPAI H5N1 that are already delineated in the NIH Guidelines. These enhancements include changes to the facility and biosafety equipment and practices, including occupational health practices. Based on the recommendations of the RAC, the NIH Office of Biotechnology Activities (OBA) concluded that more specific guidance regarding recombinant research with mammalian-transmissible HPAI H5N1 virus is warranted.

The resulting amendments to the NIH Guidelines are "Minor Actions" under Section IV-C-1-(b)-2 of the NIH Guidelines, and therefore, will be implemented immediately upon publication in the *Federal Register*. While a Minor Action only requires consultation with the RAC chair and one or more RAC members, as necessary, as noted above, these changes were developed after extensive consultation with the full RAC and other experts and were discussed at a public RAC meeting. Publication in the Federal Register will inform the scientific and biosafety communities, as well as solicit continued scientific input should revisions be needed in the future.

DATES: The public is encouraged to submit written comments on this action. Comments may be submitted to the OBA in paper or electronic form at the OBA mailing, fax, and e-mail addresses shown below under the heading "For Further Information." All comments should be submitted by [Insert date 30 days after date of publication]. All written comments received in response to this notice will be available for public inspection in the NIH OBA, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985, weekdays between the hours of 8:30 a.m. and 5 p.m. and may be posted to the OBA's website.

FOR FURTHER INFORMATION: If you have questions, or require additional information about these changes, please contact the OBA by e-mail at oba@od.nih.gov, or telephone at 301-496-9838. Comments may be submitted to the same email address or by fax at 301-496-9839 or by mail to the Office of Biotechnology Activities, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, Maryland

20892-7985. Background information may be obtained by contacting NIH OBA by email at oba@od.nih.gov.

SUPPLEMENTARY INFORMATION

BACKGROUND:

The NIH is a major funder of research on influenza viruses, much of which involves recombinant DNA technology. One important area of research is focused on currently circulating HPAI H5N1 influenza viruses. These avian influenza viruses primarily infect and kill poultry and other susceptible species. Currently, almost all HPAI H5N1 infections in humans have been linked to a person having close contact with infected poultry; the virus does not seem to transmit readily among humans. In the approximately 600 human cases of infection with HPAI H5N1 virus reported to the WHO to date, apparent human-to-human transmission is limited to small, familial clusters (see e.g., Kandun, I.N. et al. Three Indonesian Clusters of H5N1 Virus Infection in 2005, N Engl. J. M. 355: 2186-94 (2006)), without sustained chains of transmission in the community. However, the mortality rate for the human infections reported to WHO is almost 60% [http://www.who.int/influenza/human_animal_interface/EN_GIP_20130201CumulativeNumberH5N1cases.pdf]. The high mortality rate for these clinical infections is of great concern, especially if such a virus developed the ability to transmit efficiently among humans.

The public health benefits of research on potentially pandemic influenza viruses include identification of genetic changes that contribute to host adaptation, transmissibility, and

virulence. Such information can be used to enhance surveillance as well as contribute to the development of vaccine candidates, and identification of targets for antiviral drugs. While research into influenza viral virulence mechanisms and the development of vaccines and antiviral drugs are public health priorities, it is equally important that the research be performed under appropriate biocontainment to protect the health of laboratory personnel and the public.

In 2009, the NIH Guidelines were amended to address research with certain influenza viruses with increased pandemic potential, including the reconstructed 1918 H1N1 virus and HPAI H5N1 viruses of the Goose/Guangdong/96-like H5 lineage, the lineage responsible for human cases to date. Specifically, HPAI H5N1 viruses were classified as Risk Group 3 agents in Appendix B-III-D, i.e., agents that are able to cause serious or lethal disease, but for which preventative and therapeutic agents may be available (high individual risk, low community risk). In making that decision, the OBA noted that for HPAI H5N1 virus, the individual risk of serious or lethal disease is quite high; however, the community risk is currently considered low, as there is only limited evidence of human-to-human transmission.

Since 2009, the NIH Guidelines have set containment for HPAI H5N1 virus research at Biosafety Level (BL) 3 with additional enhancements. These enhancements include additional personal protective equipment (e.g., powered air-purifying respirators, protective suits) and practices and procedures (e.g., clothing changes, showers when appropriate) that are not required at BL3 containment. In addition, the NIH Guidelines

require implementation of specific practices to avoid inadvertent cross-contamination with other influenza viruses being studied in the same laboratory. The NIH Guidelines require periodic training for these enhanced practices. To address the potential public health risks of a laboratory exposure, the NIH Guidelines also set forth detailed occupational health requirements for research with each virus, including how to respond to known laboratory exposures or to the development of an influenza-like illness in laboratory workers.

Of note, there are other regulatory requirements governing research with HPAI H5N1 virus. The HPAI H5N1 influenza viruses are USDA Select Agents (9 C.F.R. 121.3(b)). The USDA Animal and Plant Health Inspection Service (APHIS) regulates as a Select Agent avian influenza viruses that demonstrate a high pathogenicity in chickens and contain a specific polybasic amino acid motif at the hemagglutinin (HA) gene cleavage site (or have an amino acid sequence at the cleavage site of the HA gene that is comparable to other highly pathogenic avian influenza viruses) (9 CFR 121.3(c)(3)). Avian influenza viruses that demonstrate evidence of attenuation in poultry can be excluded from the Select Agent list pursuant to 9 C.F.R. 121.3(e). The biosafety containment level recommended for most research with HPAI H5N1 viruses that are Select Agents is a minimum of BL3 enhanced or Animal Biosafety Level 3 (ABSL3) enhanced. Influenza viruses containing genes from an HPAI virus, which are not classified as Select Agents by the USDA, are still regulated by that Agency through "permitting" regulations (9 C.F.R. 122) that govern imports and interstate movements of the viruses. In addition, on October 17, 2012, the CDC issued a request for information

and comment regarding whether HPAI H5N1 viruses containing an HA from the Goose/Guangdong/1/96 lineage should become an HHS Select Agent (77 FR 63783). Additional containment practices may apply under the Select Agent regulations and the OBA will defer to the requirements of the regulatory agencies on restricted experiments [9 C.F.R. Sec. 121.13, 45 C.F.R. Sec. 73.13], for example, the introduction of antiviral resistance into HPAI H5N1 influenza viruses.

In light of recent publications [Imai, M. et al., Nature 486:420-428 (2012), Herfst, S. et al., Science 336:1534-1541 (2012)] reporting genetic changes that may enhance the ability of the HPAI H5N1 virus to transmit by respiratory droplets among mammals, the RAC was asked to revisit the biosafety recommendations in the October 2011 NIH Guidelines for research with HPAI H5N1 virus to determine whether these are adequate to address recombinant DNA research with mammalian-transmissible HPAI H5N1 viruses. On January 24, 2013, the RAC met in a public meeting, together with influenza experts, as well as experts from the CDC, BARDA, FDA, WHO, and USDA. The RAC concluded that all HPAI H5N1 viruses, including mammalian-transmissible viruses, are RG3 agents because vaccines and antivirals may be available for the treatment and/or prevention of disease. However, because a mammalian-transmissible virus may present increased risk to the community, additional enhancements to the current biosafety containment and practices were recommended.

The OBA accepts the recommendations of the RAC and the NIH Guidelines have been amended to include the following enhancements for research with mammalian-transmissible HPAI H5N1 virus:

- Enhancements of BL3 facilities to include 1) HEPA filtration of exhaust air and air handling systems that are designed to avoid airflow reversal during failure, with periodic verification and at least annual verification of the HEPA filters and 2) backup power for critical controls and instrumentation necessary to maintain containment;
- Specific guidance on liquid and animal waste disposal;
- A requirement that antiviral susceptibility be maintained in laboratory strains of mammalian-transmissible HPAI H5N1 influenza unless specifically authorized by the NIH or another regulatory agency, such as the CDC or USDA in their role administering the Select Agent regulations;
- Additional practices to avoid self-contamination or inadvertent release of the viruses by a laboratory worker, including the requirement for two individuals to be in the lab when certain research is being conducted;
- Enhancements to current occupational health requirements: 1) that HPAI H5N1 licensed vaccines should be taken, if available, 2) mandatory collection and storage of serum samples, 3) isolation of workers out of the community, in a medical or other appropriate facility if they have had a potential "high-risk" exposure to the virus, or for those who develop influenza-like illness after being in a laboratory in which research with the virus is being conducted, 4) active surveillance programs for influenza-like illness, 5) a prohibition for

home supplies of antiviral agents to avoid self-medication without reporting of illness; and

- A requirement that each laboratory worker sign a document acknowledging that (s)he understands and agrees to adhere to biosafety, biosecurity, and occupational health requirements and also agrees to report any potential exposures or accidents, including those made by other individuals in the laboratory.

In addition to these enhancements, all biosafety containment and practices for research with HPAI H5N1 viruses are applicable to research with mammalian-transmissible strains, and additional containment and practices for mammalian-transmissible HPAI H5N1 are specified in the NIH Guidelines. Institutions may, of course, decide to adopt the practices required for research with mammalian-transmissible HPAI H5N1 viruses for all research with HPAI H5N1 viruses.

The RAC made several general recommendations to help guide biosafety assessments for research with HPAI H5N1 influenza viruses, as well as research with emerging influenza viruses that have the potential to lead to a human pandemic because the general population is not expected to have immunity to such viruses (e.g., an H9 avian influenza virus). The OBA concurs with these general risk assessment principles and will incorporate these recommendations into a general guidance document for research with influenza, taking into account any comments received on this notice:

- While acknowledging the limits of any animal model to predict disease in humans accurately, the ferret remains the best model for assessing the pathogenicity and transmissibility of an influenza virus in mammals. Therefore, containment decisions for influenza viruses should be made based on the assumption that transmissibility and pathogenicity in this model are predictive of the disease in humans.

- It is difficult to predict which experiments may generate a mammalian-transmissible virus; however, given the pathogenicity of HPAI H5N1 viruses, if the experimental procedures are such that it could reasonably be anticipated to generate aerosols and create a mammalian transmissible HPAI H5N1 virus, such as serial passaging of an HPAI H5N1 virus in animals, these studies should be conducted at BL3 with all of the enhancements required for research with HPAI H5N1 mammalian-transmissible virus.

- Likewise, while the risk of generating a mammalian-transmissible, pathogenic influenza virus cannot always be predicted at the beginning of the experiment, enhanced BL3 containment and practices should be considered for research with any influenza virus if: 1) the virus has a high potential to cause disease in humans, as demonstrated in the ferret model, 2) there is little or no community immunity (i.e., a virus with a high pandemic risk), and 3) the research is designed to increase the ability of that influenza virus to be transmissible among mammals. A risk assessment will determine whether the most appropriate BL3 enhanced containment practices are those for RG3 influenza

viruses, or include, in addition, the specific enhancements for mammalian-transmissible HPAI H5N1 virus.

- One should also consider BL3 enhanced containment and practices for experiments involving any influenza virus for which there is little or no community immunity (high pandemic risk), if the experiment is designed to increase transmissibility in mammals by respiratory droplets, as the ability to transmit efficiently among humans is a critical attribute of pandemic influenza viruses.

Amendments to the NIH Guidelines

In order to ensure that biosafety for research involving mammalian-transmissible HPAI H5N1 virus is addressed appropriately, the OBA has made changes to the following sections of the NIH Guidelines:

In order to make it clear that all facility, procedures and practices for research with HPAI H5N1 viruses also apply to research with mammalian-transmissible HPAI H5N1 viruses, Section III-D-7 is amended to include a specific reference to mammalian-transmissible HPAI H5N1 virus.

The Section III-D-7 previously stated:

Section III-D-7. Experiments Involving Influenza Viruses

Experiments with influenza viruses generated by recombinant methods (e.g., generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific

mutations) shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus (e.g., experiments with viruses containing a majority of segments from a RG3 virus shall be conducted at BL3). Experiments with influenza viruses containing genes or segments from 1918-1919 H1N1 (1918 H1N1), human H2N2 (1957-1968) and highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1) shall be conducted at BL3 enhanced containment (see Appendix G-II-C-5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses) unless indicated below.

Section III-D-7 is amended to state:

Section III-D-7. Experiments Involving Influenza Viruses

Experiments with influenza viruses generated by recombinant methods (e.g., generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific mutations) shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus (e.g., experiments with viruses containing a majority of segments from a RG3 virus shall be conducted at BL3). Experiments with influenza viruses containing genes or segments from 1918-1919 H1N1 virus (1918 H1N1), human H2N2 virus (1957-1968) and highly pathogenic avian influenza H5N1 virus strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1), including, but not limited to strains of HPAI H5N1 virus that are transmissible among mammals by respiratory droplets, as demonstrated in an appropriate animal model or clinically in humans, (hereinafter

referred to as mammalian-transmissible HPAI H5N1 virus), shall be conducted at BL3 enhanced containment (see Appendix G-II-C-5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses) unless indicated below.

Laboratory Practices and Facilities

Appendix G-II-C outlines the requirements for BL3 facilities and containment practices. All of the requirements in G-II-C apply to research with HPAI H5N1 virus. For research with mammalian-transmissible HPAI H5N1 viruses, the OBA is adding additional facility requirements, specific guidelines for waste disposal, and a requirement that baseline serum samples shall be collected.

Appendix G-II-C-2-n previously stated:

Appendix G-II-C-2-n. All wastes from laboratories and animal rooms are appropriately decontaminated before disposal.

As amended:

Appendix G-II-C-2-n. All wastes from laboratories and animal rooms are appropriately decontaminated before disposal. For research involving mammalian-transmissible HPAI H5N1 virus, liquid effluents should be chemically disinfected or heat-treated, or collected and processed in a central effluent decontamination system. Decontamination of shower and toilet effluents is not required, provided appropriate practices and procedures are in place for primary containment of mammalian-transmissible HPAI H5N1 virus. Animal tissues, carcasses, and bedding originating from the animal room must be decontaminated

by an effective and validated method (e.g., use of an autoclave) preferably before leaving the containment barrier. If waste must be transported, special practices should be developed for transport of infectious materials to designated alternate location(s) within the facility.

Appendix G-II-C-2-r states that baseline serum samples should be collected for all laboratory and other at-risk personnel and stored. Collection of baseline serum samples is mandatory for personnel performing research with mammalian-transmissible HPAI H5N1 virus. In addition, the OBA has clarified the time-frame for storage of samples.

Appendix G-II-C-2-r previously stated:

Baseline serum samples for all laboratory and other at-risk personnel should be collected and stored. Additional serum specimens may be collected periodically depending on the agents handled or the function of the laboratory.

The revised section is amended to read as follows:

Appendix G-II-C-2-r. Baseline serum samples for all laboratory and other at-risk personnel should be collected and stored in accordance with institutional policy and at least for the time period in which the personnel continues to work with the agent at biosafety level 3 containment. Such samples must be collected and stored for laboratory and other at-risk personnel who will work with mammalian-transmissible HPAI H5N1 virus. Additional serum specimens may be collected periodically depending on the agents handled or the function of the laboratory.

Facilities

Additional facility enhancements are required for research with mammalian-transmissible HPAI H5N1 virus. These enhancements include HEPA filtration of exhaust air and specific requirements for the air handling systems. In addition, facilities working with mammalian-transmissible HPAI H5N1 virus must have backup power for critical controls. These changes are outlined in a revised Appendix G-II-C-4 Laboratory Facilities (BL3).

Specifically, Appendix G-II-C-4-i previously stated:

Appendix G-II-C-4-i. A ducted exhaust air ventilation system is provided. This system creates directional airflow that draws air into the laboratory through the entry area. The exhaust air is not recirculated to any other area of the building, is discharged to the outside, and is dispersed away from the occupied areas and air intakes. Personnel shall verify that the direction of the airflow (into the laboratory) is proper. The exhaust air from the laboratory room may be discharged to the outside without being filtered or otherwise treated.

The amended section clarifies that air flow is from uncontaminated spaces for all labs and adds the following additional requirements for research with mammalian-transmissible HPAI H5N1:

Appendix G-II-C-4-i. A ducted exhaust air ventilation system is provided. This system creates directional airflow that draws air into the laboratory from uncontaminated spaces surrounding the laboratory. The exhaust air is not recirculated to any other area of the building, is discharged to the outside, and is dispersed away from occupied areas and air intakes. Personnel shall verify that the direction of the airflow (into the laboratory) is proper. The exhaust air from the laboratory room may be discharged to the outside without being filtered or otherwise treated unless research is being conducted with mammalian-transmissible HPAI H5N1 virus. For research with mammalian-transmissible HPAI H5N1 virus, exhaust air must be HEPA filtered and there must be sealed ductwork from the containment barrier to the filter. In addition, the air handling system shall be designed such that under failure conditions, the airflow will not be reversed and periodic verification, with annual verification of the HEPA filters, shall be performed. Finally, backup power shall be available for critical controls and instrumentation necessary to maintain containment.

Appendix G-II-C-5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.

Appendix G-II-C-5 provides additional specific biosafety guidance for research with 1918 H1N1, human H2N2 (1957-1968), and HPAI H5N1 viruses and is intended to supplement the guidance provided in Appendix G, Physical Containment, and Appendix Q, Physical and Biological Containment for Recombinant DNA Research Involving Animals, which applies to large research animals. All of the practices and occupational health measures described in Appendix G-II-C-5 apply to research with mammalian-

transmissible HPAI H5N1 virus. Additional requirements for research with mammalian-transmissible HPAI H5N1 virus are specified. In addition to updating the following sections to include specific recommendations for research with mammalian-transmissible HPAI H5N1 virus, this section will specifically reference the additional practices and facilities requirements for mammalian-transmissible HPAI H5N1 virus discussed above.

Previously Appendix G-II-C-5 was just a title.

Appendix G-II-C-5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.

It is amended to read as follows:

Appendix G-II-C-5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.

(See Appendices G-II-C-2-n, G-II-C-2-r, and G-II-C-4-i for additional guidance for facilities, waste handling, and serum collection for research involving mammalian-transmissible HPAI H5N1 virus.)

Appendix G-II-C-5-a. Containment, Practices, and Training for Research with Risk Group 3 Influenza Viruses (BL3 Enhanced)

Personal Protective Equipment (PPE) and Practices. Research with HPAI H5N1 virus must be conducted using powered air purifying respirators (PAPRs), double gloves, wrap-around gowns, and shoe coverings. The RAC recommended that laboratory workers doing research with mammalian-transmissible strains of HPAI H5N1 virus also

1) use protective sleeves over the gown when working in a biosafety cabinet, 2) spray or wipe down their personal protective equipment, in particular their PAPRs, with a disinfectant that has activity against influenza virus prior to leaving containment, and 3) always take a shower before leaving the facility. In addition, at least two individuals should be present in the lab at all times while certain research is conducted and removal of PPE, prior to the shower, should be observed. This system is aimed at promoting adherence to all containment practices, including correct removal of PPE to avoid self-contamination. Finally, as part of proper training, the laboratory workers shall sign a document acknowledging their understanding of, and intent to adhere to biosafety, biosecurity, and occupational health requirements and that they agree to report any exposures or accidents, including those that do not involve the worker. The OBA agrees with these recommendations, and they are implemented through amendments to the following sections.

Appendix G-II-C-5-a-(1) previously stated:

Appendix G-II-C-5-a-(1). In addition to standard BL3 practices, the following additional personal protective equipment and practices shall be used:

1) Powered Air-purifying Respirators (PAPR) are worn.

2) Street clothes are changed to protective suit (e.g., wrap-back disposable gown, olefin protective suit).

3) Double gloves are worn.

4) Appropriate shoe coverings are worn (e.g., double disposable shoe coverings, single disposable shoe coverings if worn with footwear dedicated to BL3 enhanced laboratory

use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated).

5) Showers prior to exiting the laboratory should be considered depending on risk assessment of research activities.

The revised Appendix G-II-C-5-a-(1) now states:

Appendix G-II-C-5-a-(1). In addition to standard BL3 practices, the following additional personal protective equipment and practices shall be used:

1) Powered Air-purifying Respirators (PAPR) are worn.

2) Street clothes are changed to protective suit (e.g., wrap-back disposable gown, olefin protective suit).

3) Double gloves (disposable) are worn. For research with mammalian-transmissible HPAI H5N1 virus, protective sleeves shall be worn over the gown while working in a biosafety cabinet.

4) Appropriate shoe coverings are worn (e.g., double disposable shoe coverings, single disposable shoe coverings if worn with footwear dedicated to BL3 enhanced laboratory use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated).

5) Showers prior to exiting the laboratory should be considered depending on risk assessment of research activities, with the exception that showers prior to exiting the laboratory are required for all research with mammalian-transmissible HPAI H5N1 virus, including care of animals infected with mammalian-transmissible HPAI H5N1 virus.

(6) For research with mammalian-transmissible HPAI H5N1 virus, prior to leaving containment, personal protective equipment shall be sprayed or wiped down with a disinfectant that has activity against influenza viruses.

(7) In order to promote adherence to proper practices, including proper removal of personal protective equipment, and reporting of any loss of containment or exposures, at least two individuals should be in the laboratory at all times when research with mammalian-transmissible HPAI H5N1 virus involves experimental procedures with animals or sharps, or when procedures are being conducted whereby the generation of aerosols is reasonably anticipated. Removal of personal protective equipment should be observed.

Appendix G-II-C-5-a-(2) previously stated:

Appendix G-II-C-5-a-(2). As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially the proper use of respiratory equipment, such as PAPRs, and clothing changes, is required.

The revised Appendix G-II-C-5-a-(2) now states:

Appendix G-II-C-5-a-(2). As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially the proper use of respiratory equipment, such as PAPRs, and clothing changes, are required. For research with mammalian-transmissible HPAI H5N1 virus, laboratory workers shall be required to sign a document acknowledging their

understanding of and intent to adhere to biosafety, biosecurity, and occupational health requirements. This document shall include a statement that the laboratory worker agrees to report any exposures or accidents, including those by other individuals in the lab.

Anti-viral susceptibility. Currently, there is one FDA-licensed vaccine against a single clade of HPAI H5N1 virus, although others with adjuvants to induce broader and more prolonged immune responses are in clinical trials. As vaccines are not 100 percent effective and the mortality rate for HPAI H5N1 virus infections in humans is currently close to 60 percent, the RAC concluded that the availability of effective antiviral agents is a critical pre-requisite for conducting this research at BL3 enhanced containment. Therefore, as stated in Section III-D-7-d, any experiment that attempts to create a mammalian-transmissible virus that is also resistant to neuraminidase inhibitors, including oseltamivir, or other effective antivirals agents (including investigational antiviral agents), would need to be reviewed by the appropriate federal authorities, i.e., the NIH Director or Select Agent Program officials. It is also important to maintain antiviral sensitivity throughout experiments with mammalian-transmissible HPAI H5N1 virus. Therefore, the Appendix G-II-C-5-a-(5) has been amended to address this issue.

Appendix G-II-C-5-a-(5) previously stated:

Appendix G-II-C-5-a-(5). Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968) to antiviral agents shall be established by sequence analysis or suitable

biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed.

The revised Appendix G-II-C-5-a-(5) now states:

Appendix G-II-C-5-a-(5). Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968) to antiviral agents shall be established by sequence analysis or suitable biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed. If susceptibility to neuraminidase inhibitors or other effective antiviral agents is lost as a result of genetic modification or serial passage of a mammalian-transmissible HPAI H5N1 virus, then any research with this antiviral agent-resistant virus shall be stopped and research shall only proceed after review by the NIH (as outlined in Section III-A-1-a) or the appropriate federal regulatory agency.

Occupational Health Measures. The NIH Guidelines contain detailed occupational health requirements for research with HPAI H5N1 virus. Each institution is required to develop an occupational health plan that includes a requirement for seasonal flu vaccine, a plan to report all incidents (i.e., spills, accidents and potential exposures), and procedures to isolate and treat those who develop influenza-like illness (e.g., fever or respiratory illness) or those who have an accident in the laboratory that places them at high risk of exposure to the virus. The RAC made additional recommendations for research with mammalian-transmissible HPAI H5N1 virus to

minimize the potential public health risks that could result from a laboratory worker becoming infected with one of these viruses and entering the community. If a laboratory worker has a respiratory or mucous membrane exposure to a mammalian-transmissible HPAI H5N1 virus, that worker shall be isolated in a hospital room or other designated facility away from the public until infection can be ruled out, as is required in the NIH Guidelines for research with the 1918 H1N1 influenza virus. The RAC also recommended that if a licensed vaccine against HPAI H5N1 virus is available, and there are no medical contraindications, it should be taken by all laboratory workers performing research with mammalian-transmissible HPAI H5N1, and a post-vaccination serum sample shall be collected for evaluation of immune responses and stored. Antiviral agents for treating potential exposures shall only be provided after medical evaluation; home supplies shall not be provided to avoid self-treatment of influenza-like illness without seeking medical care. Finally, an active surveillance program to identify laboratory workers with influenza-like illness shall be undertaken. To implement these changes, the following sections are amended.

Appendix G-II-C-5-c outlines the requirement for an influenza-specific occupational health plan that needs to be developed prior to work with any RG3 influenza virus, including HPAI H5N1 virus. In reviewing Appendix G-II-C-5-c, the RAC noted that clarification of the wording of Appendix G-II-C-5-c was needed to define what an incident includes and the time frames for reporting. This change will apply to all research with RG3 influenza viruses, which includes HPAI H5N1 virus, as well as

research with 1918 H1N1 and influenza viruses containing the HA from the H2N2 virus that circulated from 1957-1968.

Appendix G-II-C-5-c previously stated:

Appendix G-II-C-5-c: A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (e.g., local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan should include an incident reporting system and laboratory workers shall report all incidents.

The revised Appendix G-II-C-5-c states:

Appendix G-II-C-5-c. Occupational Health

A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (e.g., local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan shall include a description of the incident reporting system in place for incidents, which includes any loss of containment, spills, accidents, or potential exposures. The plan must specify that all incidents must be reported immediately to the appropriate institutional authorities, and no later than 24 hours to the appropriate public health authorities (e.g., the U.S. Department of Agriculture, the Centers for Disease Control and Prevention, NIH, local and state health authorities).

Appendix G-II-C-5-c-(2) previously stated:

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall include:

1) Unless there is a medical contraindication to vaccination (e.g., severe egg allergy) annual seasonal influenza vaccination as prerequisite for research to reduce risk of influenza like illness requiring isolation and tests to rule out infection with experimental virus and possible co-infection with circulating influenza strains.
2) Virus specific vaccination, if available, should be offered.
3) Reporting of all respiratory symptoms and/or fever (i.e., influenza like illnesses);
4) 24-hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and is able to provide appropriate antiviral agents. Real-time reverse transcription-polymerase chain reaction (RT-PCR) procedures should be used to discriminate these viruses from currently circulating human influenza viruses. For exposures to viruses containing genes from 1918 H1N1 or the HA gene from human H2N2 (1957-1968), specimens shall be sent to the CDC for testing (RT-PCR and confirmatory sequencing).

The revised Appendix G-II-C-5-(2) now states:

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall include:

1) Unless there is a medical contraindication to vaccination (e.g., a severe egg allergy), annual seasonal influenza vaccination as a prerequisite for research to reduce the risk of influenza-like illness that would require isolation and testing to

rule out infection with experimental viruses and raise the risk for possible co-infection with circulating influenza strains.

2) Virus-specific vaccination, if available, should be offered and if a licensed HPAI H5N1 vaccine is available, and there are no medical contraindications, laboratory workers performing research with mammalian-transmissible HPAI H5N1 viruses should be vaccinated. A post-vaccination serum sample shall be collected, assessed for immune response, and stored in accordance with institutional policy, at least for the time in which the laboratory worker continues to conduct HPAI H5N1 virus research.

3) Reporting of all respiratory symptoms and/or fever (i.e., influenza like illnesses). For research involving mammalian-transmissible HPAI H5N1 virus, laboratory workers shall be actively monitored for influenza-like illness (i.e., fever and respiratory symptoms).

4) 24-hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and is able to provide appropriate antiviral agents. Real-time reverse transcription polymerase chain reaction (RT-PCR) assays should be used for virus detection and to discriminate these viruses from currently circulating human influenza viruses. For exposures to viruses containing genes from 1918 H1N1 or the HA gene from human H2N2 (1957-1968), specimens shall be sent to the CDC for testing (RT-PCR and confirmatory sequencing).

When the NIH Guidelines were revised in 2009, Appendix G-II-C-5-c-(2) was added to specify the development of a detailed occupational health plan for research with each RG3 influenza virus. The community risk from an inadvertent laboratory release of an influenza virus containing the HA gene from human H2N2 (1957-1968) or gene from 1918 H1N1, both of which have previously caused pandemics, was expected to be higher than for wild-type HPAI H5N1 virus, which does not efficiently transmit human-to-human. Consequently, the previous occupational health recommendations in the NIH Guidelines differed between HPAI H5N1 virus, and H2N2 (1957-1968) or 1918 H1N1 viruses. For 1918 H1N1 and H2N2 (1957-1968) viruses, which were demonstrated to efficiently transmit from person-to-person, isolation outside of the community of a laboratory worker who was potentially infected with one of these viruses was determined to be an important public health measure to prevent a new pandemic with a laboratory-created virus. Home isolation was not considered a reliable public health measure as the laboratory worker could more easily leave their house or other people could enter the house. However, at the time the 2009 revisions were developed, HPAI H5N1 virus could not easily transmit among humans, and therefore, home isolation was permitted after exposure. Because the transmission of an influenza virus by respiratory droplets among ferrets indicates that this virus may also transmit among humans, the RAC recommended that isolation policies for exposures to HPAI H5N1 viruses that are transmissible by respiratory droplets among ferrets be the same as for other RG3 influenza viruses that have the ability to transmit among humans. For the same reasons, home supplies of antivirals shall not be given to laboratory workers engaged in research with mammalian-transmissible HPAI H5N1 virus to prevent self-treatment of influenza-like illness or

underreporting of potential exposures. In addition, since the phrase "antiviral agents for post-exposure prophylaxis" can be interpreted as recommending a specific approved dose, the term prophylaxis is removed because the appropriate dose is determined by the medical evaluation. The following changes were made to Appendices G-II-C-5-c-(3), G-II-C-5-c-(4), and G-II-C-5-c-(6).

Appendix G-II-C-5-c-(3) stated:

Appendix G-II-C-5-c-(3). In preparing to perform research with 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1, principal investigators should develop a clear plan specifying who will be contacted in the event of a potential exposure (during and after work hours) to conduct a risk assessment and make decisions as to the required response, including the need for and extent of isolation of the exposed worker. After any kind of potential exposure, a rapid risk assessment shall be performed by the principal investigator, health and biosafety officials, and subsequent actions should depend on the appraised level of risk of respiratory infection for the individual and potential for transmission to others. A laboratory worker performing research with either an influenza virus containing the HA gene from human H2N2 or an influenza virus containing genes and/or segments from 1918 H1N1, shall be informed in advance that, in the case of a known laboratory exposure with a high risk for infection, e.g., involving the upper or lower respiratory tract or mucous membranes, the laboratory worker will need to be isolated in a predetermined facility, rather than home isolation, until infection can be ruled out by testing (e.g., negative RT-PCR for 1918 H1N1 or human H2N2 (1957-1968)) of appropriately timed specimens. Laboratory workers shall be informed in

advance that in the case of a known laboratory exposure to highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage with high risk for infection, they should be prepared to self isolate (for example at home) until infection can be ruled out by testing (e.g., negative RT-PCR for HPAI H5N1) of appropriately timed specimens. The action taken for other types of exposures should be based on the risk assessment. In addition, based on the risk assessment: (1) treatment with appropriate antiviral agents shall be initiated, and (2) the appropriate public health authorities shall be notified.

The revised Appendix G-II-C-5-c-(3) now states:

Appendix G-II-C-5-c-(3). In preparing to perform research with 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1, principal investigators should develop a clear plan specifying who will be contacted in the event of a potential exposure (during and after work hours) to conduct a risk assessment and make decisions as to the required response, including the need for and extent of isolation of the exposed worker. After any kind of potential exposure, a rapid risk assessment shall be performed by the principal investigator, health and biosafety officials, and subsequent actions should depend on the appraised level of risk of respiratory infection for the individual and potential for transmission to others. A laboratory worker performing research with either an influenza virus containing the HA gene from human H2N2 or an influenza virus containing genes and/or segments from 1918 H1N1 or mammalian-transmissible HPAI H5N1 viruses, shall be informed in advance that, in the case of a known laboratory exposure with a high risk for infection, e.g., involving the upper or lower respiratory tract or mucous

membranes, the laboratory worker will need to be isolated in a predetermined facility, rather than home isolation, until infection can be ruled out by testing (e.g., negative RT-PCR for 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1) of appropriately timed specimens. Laboratory workers with a known laboratory exposure with high risk for infection during research with HPAI H5N1 virus strains that are not transmissible among mammals should be prepared to self-isolate (for example at home) until infection can be ruled out by testing (e.g., RT PCR for HPAI H5N1) of appropriately timed specimens. The action taken for other types of exposures should be based on the risk assessment. In addition, based on the risk assessment: (1) treatment with appropriate antiviral agents shall be initiated, and (2) the appropriate public health authorities shall be notified.

Appendix G-II-C-5-c-(4) is amended to clarify that this section applies to all individuals who enter a laboratory where research with RG3 influenza viruses is being conducted, including trainees and other employees, and not limited to those who have had a specific exposure due to loss of containment. Recognizing this clarification will likely lead to an increase in reporting of minor viral symptoms, we have also clarified that transportation to receive medical treatment and any decision on isolation is to be based on the risk assessment by the individuals identified in the occupational health plan.

Appendix G-II-C-5-c-(4) previously stated:

Appendix G-II-C-5-c-(4). Influenza-like illness. If a laboratory worker, who had recent exposure (within ten days) to influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or to animals exposed to

such viruses, demonstrates symptoms and/or signs of influenza infection (e.g., fever/chills, cough, myalgias, headache), then the lab worker shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan. The laboratory worker shall be transported to a healthcare facility that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus. The appropriate public health authorities shall be informed whenever a suspected case is isolated.

Appendix G-II-C-5-c-(4) is amended to state:

Appendix G-II-C-5-c-(4). Influenza-like illness. If an individual has entered (within ten days) a laboratory conducting research with influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or housing animals exposed to such viruses, and the individual demonstrates symptoms and/or signs of influenza infection (e.g., fever/chills, cough, myalgia, headache), then he/she shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan. If needed, the person with influenza-like illness shall be transported to a healthcare facility, under the appropriate isolation conditions, that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus. The appropriate public health authorities shall be informed whenever a suspected case is isolated.

Appendix G-II-C-5-c-(6) previously stated:

Appendix G-II-C-5-c-(6). Antiviral agents for post-exposure prophylaxis shall be provided only after medical evaluation. Home supplies shall not be provided in advance for research with 1918 H1N1 or influenza viruses containing the HA gene from human H2N2.

The revised G-II-C-5-c-(6) now states:

Appendix G-II-C-5-c-(6). Antiviral agents for an exposure shall be provided only after medical evaluation. Home supplies shall not be provided in advance for research with 1918 H1N1, mammalian-transmissible HPAI H5N1 or influenza viruses containing the HA gene from human H2N2.

Summary of Changes

The following provides the revised language for amended sections discussed above:

Section III-D-7:

Experiments with influenza viruses generated by recombinant methods (e.g., generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific mutations) shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus (e.g., experiments with viruses containing a majority of segments from a RG3 virus shall be conducted at BL3). Experiments with influenza viruses containing genes or segments from 1918-1919 H1N1 virus (1918 H1N1), human H2N2 virus (1957-1968) and highly pathogenic avian influenza H5N1 virus strains within the

Goose/Guangdong/96-like H5 lineage (HPAI H5N1), including, but not limited to, strains of HPAI H5N1 virus that are transmissible among mammals by respiratory droplets, as demonstrated in an appropriate animal model or clinically in humans (hereinafter referred to as mammalian-transmissible HPAI H5N1 virus), shall be conducted at BL3 enhanced containment (see Appendix G-II-C-5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses) unless indicated below.

Appendix G-II-C-2-n.

All wastes from laboratories and animal rooms are appropriately decontaminated before disposal. For research involving mammalian-transmissible HPAI H5N1 virus, liquid effluents should be chemically disinfected or heat-treated, or collected and processed in a central effluent decontamination system. Decontamination of shower and toilet effluents is not required, provided appropriate practices and procedures are in place for primary containment of mammalian-transmissible HPAI H5N1 virus. Animal tissues, carcasses, and bedding originating from the animal room must be decontaminated by an effective and validated method (e.g., use of an autoclave) preferably before leaving the containment barrier. If waste must be transported, special practices should be developed for transport of infectious materials to designated alternate location(s) within the facility.

Appendix G-II-C-2-r:

Baseline serum samples for all laboratory and other at-risk personnel should be collected and stored in accordance with institutional policy and at least for the time period in which the personnel continues to work with the agent at biosafety level 3 containment. Such

samples must be collected and stored for laboratory and other at risk personnel who will work with mammalian-transmissible HPAI H5N1 virus. Additional serum specimens may be collected periodically depending on the agents handled or the function of the laboratory.

Appendix G-II-C-4-i.

A ducted exhaust air ventilation system is provided. This system creates directional airflow that draws air into the laboratory from uncontaminated spaces surrounding the laboratory. The exhaust air is not recirculated to any other area of the building, is discharged to the outside, and is dispersed away from occupied areas and air intakes. Personnel shall verify that the direction of the airflow (into the laboratory) is proper. The exhaust air from the laboratory room may be discharged to the outside without being filtered or otherwise treated unless research is being conducted with mammalian-transmissible HPAI H5N1 virus. For research with mammalian-transmissible HPAI H5N1 virus, exhaust air must be HEPA filtered and there must be sealed ductwork from the containment barrier to the filter. In addition, the air handling system shall be designed such that under failure conditions, the airflow will not be reversed and periodic verification, with annual verification of the HEPA filters, shall be performed. Finally, backup power shall be available for critical controls and instrumentation necessary to maintain containment.

Appendix G-II-C-5. Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.

(See Appendices G-II-C-2-n, G-II-C-2-r, and G-II-C-4-i for additional guidance for facilities, waste handling, and serum collection for research involving mammalian-transmissible HPAI H5N1 virus.)

Appendix G-II-C-5-a. Containment, Practices, and Training for Research with Risk Group 3 Influenza Viruses (BL3 Enhanced)

Appendix G-II-C-5-a-(1).

In addition to standard BL3 practices, the following additional personal protective equipment and practices shall be used:

1) Powered Air-purifying Respirators (PAPR) are worn.

2) Street clothes are changed to protective suit (e.g., wrap-back disposable gown, olefin protective suit).

3) Double gloves (disposable) are worn. For research with mammalian-transmissible HPAI H5N1 viruses, protective sleeves shall be worn over the gown while working in a biosafety cabinet.

4) Appropriate shoe coverings are worn (e.g., double disposable shoe coverings, single disposable shoe coverings if worn with footwear dedicated to BL3 enhanced laboratory use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated).

5) Showers prior to exiting the laboratory should be considered depending on risk assessment of research activities, with the exception that showers prior to exiting the

laboratory are required for all research with mammalian-transmissible HPAI H5N1 virus, including care of animals infected with mammalian-transmissible HPAI H5N1 virus.

(6) For research with mammalian-transmissible HPAI H5N1 virus, prior to leaving containment, personal protective equipment shall be sprayed or wiped down with a disinfectant that has activity against influenza viruses.

(7) In order to promote adherence to proper practices, including proper removal of personal protective equipment, and reporting of any loss of containment or exposures, at least two individuals should be in the laboratory at all times when research with mammalian-transmissible HPAI H5N1 virus involves experimental procedures with animals or sharps, or when procedures are being conducted whereby the generation of aerosols is reasonably anticipated. Removal of personal protective equipment should be observed.

Appendix G-II-C-5-a-(2).

As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially the proper use of respiratory equipment, such as PAPRs, and clothing changes, are required. For research with mammalian-transmissible HPAI H5N1 virus, laboratory workers shall be required to sign a document acknowledging their understanding of and intent to adhere to biosafety, biosecurity, and occupational health requirements. This document shall include a statement that the laboratory worker agrees to report any exposures or accidents, including those by other individuals in the lab.

Appendix G-II-C-5-a-(5).

Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968) to antiviral agents shall be established by sequence analysis or suitable biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed. If susceptibility to neuraminidase inhibitors or other effective antiviral agents is lost as a result of genetic modification or serial passage of a mammalian-transmissible HPAI H5N1 virus, then any research with this antiviral agent-resistant virus shall be stopped and research shall only proceed after review by the NIH (as outlined in Section III-A-1-a) or the appropriate federal regulatory agency.

Appendix G-II-C-5-c. Occupational Health

A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (e.g., local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan shall include a description of the incident reporting system in place for incidents, which includes any loss of containment, spills, accidents, or potential exposures. The plan must specify that all incidents must be reported immediately to the appropriate institutional authorities, and no later than 24 hours to the appropriate public health authorities (e.g., the U.S. Department of Agriculture, the Centers for Disease Control and Prevention, NIH, local and state health authorities).

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall include:

1) Unless there is a medical contraindication to vaccination (e.g., a severe egg allergy), annual seasonal influenza vaccination as a prerequisite for research to reduce the risk of influenza-like illness that would require isolation and testing to rule out infection with experimental viruses and raise the risk for possible co-infection with circulating influenza strains.
2) Virus-specific vaccination, if available, should be offered and if a licensed HPAI H5N1 vaccine is available, and there are no medical contraindications, laboratory workers performing research with mammalian-transmissible HPAI H5N1 virus should be vaccinated. A post-vaccination serum sample shall be collected, assessed for immune response, and stored in accordance with institutional policy, at least for the time in which the laboratory worker continues to conduct HPAI H5N1 virus research.
3) Reporting of all respiratory symptoms and/or fever (i.e., influenza-like illnesses). For research involving mammalian-transmissible HPAI H5N1 virus, laboratory workers shall be actively monitored for influenza-like illness (i.e., fever and respiratory symptoms).
4) 24-hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and is able to provide appropriate antiviral agents. Real-time reverse transcription polymerase chain reaction (RT-PCR) assays should be used for virus detection and to discriminate these viruses from currently circulating human influenza viruses. For exposures to viruses containing genes from 1918 H1N1 or the HA gene from human H2N2 (1957-

1968), specimens shall be sent to the CDC for testing (RT-PCR and confirmatory sequencing).

Appendix G-II-C-5-c-(3).

In preparing to perform research with 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1, principal investigators should develop a clear plan specifying who will be contacted in the event of a potential exposure (during and after work hours) to conduct a risk assessment and make decisions as to the required response, including the need for and extent of isolation of the exposed worker. After any kind of potential exposure, a rapid risk assessment shall be performed by the principal investigator, health and biosafety officials, and subsequent actions should depend on the appraised level of risk of respiratory infection for the individual and potential for transmission to others. A laboratory worker performing research with either an influenza virus containing the HA gene from human H2N2 or an influenza virus containing genes and/or segments from 1918 H1N1 or mammalian-transmissible HPAI H5N1 viruses, shall be informed in advance that, in the case of a known laboratory exposure with a high risk for infection, e.g., involving the upper or lower respiratory tract or mucous membranes, the laboratory worker will need to be isolated in a predetermined facility, rather than home isolation, until infection can be ruled out by testing (e.g., negative RT-PCR for 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1) of appropriately timed specimens. Laboratory workers with a known laboratory exposure with high risk for infection during research with HPAI H5N1 virus strains that are not transmissible among mammals should be prepared to self-isolate (for example at home) until infection can be ruled out by testing

(e.g., RT PCR for HPAI H5N1) of appropriately timed specimens. The action taken for other types of exposures should be based on the risk assessment. In addition, based on the risk assessment: (1) treatment with appropriate antiviral agents shall be initiated, and (2) the appropriate public health authorities shall be notified.

Appendix G-II-C-5-c-(4). Influenza-like illness.

If an individual has entered (within ten days) a laboratory conducting research with influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or housing animals exposed to such viruses, and the individual demonstrates symptoms and/or signs of influenza infection (e.g., fever/chills, cough, myalgia, headache), then he/she shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan. If needed, the person with influenza-like illness shall be transported, under the appropriate isolation conditions, to a healthcare facility that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus. The appropriate public health authorities shall be informed whenever a suspected case is isolated.

Appendix G-II-C-5-c-(6).

Antiviral agents for an exposure shall be provided only after medical evaluation. Home

supplies shall not be provided in advance for research with 1918 H1N1, mammalian-transmissible HPAI H5N1 or influenza viruses containing the HA gene from human H2N2.

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